Benign Prostatic Hyperplasia

Prostate Size: Does It Matter?

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Occasionally, one can witness, in a relatively short period, a significant change in either a diagnostic or a therapeutic approach to a certain condition. Such changes may be triggered by a very important basic research finding or a number of clinical observations that when taken together, convincingly demonstrate the validity of a new concept. One such example is the issue of prostate size and its role in the diagnostic evaluation of, and the therapeutic decision making in, men with lower urinary tract symptoms (LUTS) and clinical benign prostatic hyperplasia (BPH).

In the past, urologists often assessed the prostate by such imaging modalities as urethrocystoscopy, intravenous urography, voiding cystourethrography, or retrograde urethrography; if the prostate was significantly enlarged, surgery was indicated. A more recent position has been that prostate size is completely unimportant in determining the need for treatment. The 1994 Agency for Health Care Policy (AHCPR) BPH treatment guideline, in fact, recommended prostate size measurement as "optional testing to plan an invasive procedure, and not to be used to determine the need for treatment."[1] The guideline stated that urethrocystoscopy or transabdominal bladder/prostate ultrasonography—to help surgeons plan prostate surgery or balloon dilation by determining prostate size and configuration—would be the appropriate tests to conduct in this setting. This was the only mention of prostate size included in the guideline.

In the same document, a chapter on future research needs in natural history and epidemiology emphasized the need to "define the natural history of untreated BPH (progression) in terms of the probabilities and rates of further prostatic enlargement; changes in symptom severity, uroflow, and measures of urodynamic obstruction; urinary retention, infection; bladder dysfunction; and renal insufficiency," and to "determine whether disease progression (worsening of symptoms or development of complications) can be predicted by baseline assessment of symptoms, prostate size, uroflow, residual urine, or degree of urodynamic obstruction."

In this context, it is worthwhile to review a sequence of articles published during the past 12 months that at least partly address the challenge set forth by the AHCPR guideline panel.

Reference

1. McConnell JD, Barry MJ, Bruskewitz RC, et al. *Clinical Practice Guideline Number 8: Benign Prostatic Hyperplasia: Diagnosis and Treatment*. Rockville, Md: US Dept of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 94-0582.

Serum Prostate-Specific Antigen as a Predictor of Prostate Volume in Men With Benign Prostatic Hyperplasia

Roehrborn CG, Boyle P, Gould AL, Waldstreicher J.
Urology. 1999;53:581-589.

This study was prompted by several observations related to prostate size and the response to treatment with the 5α-reductase inhibitor finasteride. A meta-analysis of all 1-year, randomized, placebo-controlled trials of finasteride had shown that the therapeutic response to finasteride is somewhat dependent on baseline prostate volume.[1] In fact, this meta-analysis predicted that a prostate volume (measured by either MRI or transrectal ultrasonography) greater than 30 g suggested a statistically superior response in terms of both symptom score and flow rate when compared with placebo. It was also evident from a review of the literature that digital rectal examination (DRE) alone was insufficient in determining thresholds of prostatic enlargement. Rather, DRE tends to underestimate prostate size, and the degree of underestimation increases with increasing prostate volume.

The present study focused on a database of 4627 patients from either BPH or safety trials for whom baseline data regarding age, prostate volume, and serum prostate-specific antigen (PSA) level were available. When relating either prostate volume or serum PSA level to age, log-linear relationships were identified. In fact, the slope of the relationship between age and log-serum PSA was found to be 0.027 ± 0.0019, and the slope of the relationship between age and log-prostate volume was found to be 0.014 ± 0.001 for men in the BPH trials. This corresponded to a 14% increase in prostate volume with each decade of life. Overall, the result suggested that while prostate size increases throughout adulthood, PSA levels do not tend to increase with age until after age 40. Given the log-linear increase of prostate volume and serum PSA level with increasing age (at least in the BPH population in question), it appeared reasonable to investigate the relationship between serum PSA level and prostate volume with regard to whether serum PSA could be used to predict thresholds

of prostatic enlargement.

Several statistical and mathematical computations were performed to address this issue. First, it was observed that the expected prostate volume corresponding to a given serum PSA depends on the age of the patient, with older patients having a greater increase in prostate volume per unit of PSA. The diagnostic utility of serum PSA for identifying patients with prostate volumes above a specified threshold was evaluated using receiver operating characteristic curve analysis. The area under the curve ranged from 71% to 78%, indicating that for each given decade of life and for each threshold of prostate enlargement, PSA performs reasonably well in identifying men with enlarged glands. Another way of looking at these data is to determine PSA values for each decade of life that, with reasonable clinical certainty, would predict that the prostate was above a certain threshold. For example, to achieve a specificity of 70% while maintaining a sensitivity between 65% and 70%, approximate age-specific criteria for detecting men with prostate glands exceeding 30 mL are PSAs greater than 1.3, 1.5, or 1.7 ng/mL for men in their 50s, 60s, and 70s, respectively. To predict, with the same clinical certainty, a prostate volume of more than 40 mL, the PSA threshold for these same decades of life would be higher than 1.6, 2.0, and 2.4 ng/mL, respectively.

This study established, for the first time, a clinically useful relationship between prostate volume and serum PSA level. It justified the use of prostate volume and serum PSA level interchangeably to analyze the natural history and progression of the disease.

Reference

1. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology.* 1996;48:398-409.

Serum Prostate-Specific Antigen and Prostate Volume Predict Long-Term Changes in Symptoms and Flow Rate: Results of a Four-Year, Randomized Trial Comparing Finasteride Versus Placebo

Roehrborn CG, Boyle P, Bergner D, et al, for the PLESS Study Group.

Urology. 1999;54:662-669.

An appropriate database to look at the issues described above is the one from the PLESS (Proscar Long-Term Efficacy and Safety Study) trial, in which 3040 men are participating. Patients with a maximum urinary flow rate of 15 mL or less at a voided volume of 150 mL or more, an enlarged prostate gland by DRE, and a serum PSA level at baseline lower than 10 ng/mL were enrolled in this 4-year study and randomized to receive either finasteride (5 mg) or placebo daily. In an exploratory analysis, patients were divided into tertiles both by prostate volume (10% of patients in both placebo and finasteride arms had yearly prostate volume measurements by MRI) and by serum PSA level, which was available for all 3040 patients. Mean prostate volume at baseline for the overall group was 55 ± 26 mL, and mean serum PSA level was 2.8 ± 2.1 ng/mL. By dividing the population into thirds based on either prostate volume or serum PSA level, the following groups were established:

Parameter	Mean ± SD (mL)	N
Prostate volume (mL)		
Overall	55 ± 26	155
First tertile (14 - 41)	32.5 ± 6.3	45
Second tertile (42 - 57)	48.9 ± 4.9	60
Third tertile (58 - 150)	81.4 ± 28.9	50
Serum PSA (ng/mL)		
Overall	2.8 ± 2.1	1,498
First tertile (0.2 - 1.3)	0.86 ± 0.3	511
Second tertile (1.4 - 3.2)	2.24 ± 0.6	514
Third tertile (3.3 - 12.0)	5.36 ± 1.7	473

PSA, prostate-specific antigen.

As in all clinical research studies, the placebo-treated patients responded with a favorable change in both symptom score and flow rate, a well-known placebo effect attributable partly to a unilateral regression to the mean and partly to the fact that the patient is enrolled in a study and has a physician and a nurse coordinator taking care of and paying attention to him. In addition, the patient is unaware that during the lead-in phase, all participants receive inactive placebo medication. Patients in all PSA- and prostate-volume–based tertiles experienced a similar placebo response but differed significantly in terms of changes in symptom and urinary flow rate during the remaining years of the study. While patients in the lowest PSA tertile had an overall decrease in symptom score of −2.4 points at the end of the study, patients in the highest PSA tertile had a decrease of only −0.2 points at the end of the study. Similarly, patients in the highest prostate volume tertile experienced a decrease of only −0.7 points at the end of the study, while those in the lowest prostate volume tertile had a decrease of −2.1 points from baseline. In regard to urinary flow rate changes, the findings were equally striking. The lowest PSA tertile patients experienced an overall improvement of 1.0 mL/s from baseline at the end of the study. The middle tertile patients had an initial placebo response and then a deterioration to baseline such that at the end of the study, there was no change from baseline regarding maximum urinary flow rate. In contrast, patients in the highest PSA tertile expe-

Parameter	Lowest tertile	Middle tertile	Highest tertile
		Serum PSA	
Spontaneous retention	1.4%	2.5%	7.6%
Precipitated retention	1.5%	3.3%	4.0%
Combined retention	2.9%	5.8%	11.6%
Surgery for BPH	6.2%	9.9%	14.6%
Surgery or retention	7.9%	12.6%	19.9%
		Prostate volume	
Spontaneous retention	0.0%	1.7%	6.0%
Precipitated retention	4.4%	3.3%	8.0%
Combined retention	4.4%	5.0.%	14.0%
Surgery	6.7%	8.3%	14.0%
Surgery or retention	11.1%	11.7%	22.0%

PSA, prostate-specific antigen; BPH, benign prostatic hyperplasia.

rienced an initial placebo response, a deterioration of their flow rate thereafter and, at the end of the study, a net decrease in maximum urinary flow rate from baseline of −1.0 mL/s. Thus, by the end of the study, the difference between the placebo-treated patients in the lowest versus the highest PSA tertile was 2.0 mL/s.

This analysis demonstrated that over time, both prostate volume and serum PSA are highly predictive of the natural history of both the symptoms and the urinary flow rate changes in untreated (or placebo-treated) patients.

Reference

1. McConnell JD, Bruskewitz R, Walsh P, et al, and the PLESS Study Group. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med.* 1998;338:557-563.

Affect of Finasteride on Bother and Other Health-Related Quality of Life Aspects Associated with BPH

Bruskewitz R, Girman CJ, Fowler J, et al, for the PLESS Study Group.
Urology. 1999;54:670-678.

From the same PLESS database, PSA-stratified changes in bother and other health-related quality-of-life scores and in sexual function and satisfaction scores were analyzed. In the study population, the placebo-treated patients experienced a decrease in the bother score (range, 0 to 28 points; baseline, approximately 14.7 points) of about −1.2 points, while the finasteride-treated patients experienced a decrease of −3.0 points ($P < .001$). When stratifying the populations again by PSA tertiles, however, it was evident that the patients in the lowest PSA tertile had a sustained placebo response of approximately −2 points throughout the study, while the patients in the middle and higher PSA tertiles deteriorated toward baseline over time and ended with a decrease from baseline of −0.8 and −0.6, respectively, at the end of the study.

Concerning the interference score (range, 0 to 28 points; baseline mean, 8.5 and 8.3 for finasteride and placebo, respectively), the mean improvement after 4 years was −2.5 points for finasteride and −1.2 for placebo ($P < 0.01$). Again, when stratifying the population by PSA tertiles, it became evident that patients in the lowest PSA tertile had a sustained placebo response of approximately −1.8 points, while those in the middle and higher PSA tertiles deteriorated toward baseline and experienced a change from baseline of −1.1 and −0.8 points only.

A very similar phenomenon—namely, a numerically more significant worsening from baseline for the patients with higher PSAs at baseline—was noted for the sexual activity question, the sexual frequency question, and the perception of general health question.

Serum Prostate-Specific Antigen Concentration Is a Powerful Predictor of Acute Urinary Retention and Need for Surgery in Men With Clinical Benign Prostatic Hyperplasia

Roehrborn CG, McConnell JD, Lieber M, et al, for the PLESS Study Group.
Urology. 1999;53:473-480.

Lastly, the PLESS trial database also served as a means to analyze—by volume and serum PSA level—the likelihood that patients will either experience episodes of acute urinary retention or have to undergo prostate surgery over the course of the study's 4 years.

It is clear that the incidence either of spontaneous or pre-

cipitated retention or of surgery increases with increasing serum PSA level and/or baseline volume.

While the tertile analysis based on either serum PSA or prostate volume was a somewhat arbitrary categorization of the patient population, it proved to be useful in separating patients at lower and higher risk regarding symptom, bother, and flow rate changes. Additional analyses were done regarding the risk of retention or surgery. When plotting the incidences of spontaneous or precipitated retention or BPH-related surgery over a period of 4 years by incremental baseline serum PSA level, it is evident that the risk increases linearly with increasing baseline serum PSA level.

The AHCPR Guideline Panel challenged the urologic community to better define the natural history of untreated BPH in terms of changes in symptom severity, flow rate, and urinary retention and to determine whether disease progression (ie, worsening of symptoms or development of complications) could be predicted by baseline parameters.

The collection of articles reviewed here demonstrates that prostate volume and (as a proxy parameter) serum PSA level are useful baseline criteria by which to stratify patients presenting with LUTS and clinical BPH into those with lower and higher risk of progression in terms of all parameters, including symptom, bother, urinary flow rate, and the risk of retention or surgery. Thus, when patients present with LUTS and BPH, prostate volume and/or serum PSA level are useful in determining the need for treatment and, perhaps, the choice of treatment.

Erectile Dysfunction

Premature Ejaculation: Prevalent but Poorly Understood

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One of the least understood areas of urology and sexual dysfunction is ejaculation, the process by which the ejaculate, once it is deposited into the posterior urethra (seminal emission), is transported in an antegrade fashion out of the urethra. In the male, orgasm is the sensory perception of the ejaculatory response. Disorders of ejaculation can be divided into 3 main categories: anejaculation (inability to ejaculate and, by assumption, to experience orgasm), retrograde ejaculation (ejaculate goes into the bladder, but orgasm is still appreciated), and premature ejaculation (PE) (ejaculation and orgasm occur but much sooner than the patient and/or partner desires). This review will focus on PE and encompass a number of complementary studies.

Penile Sensitivity in Men With Premature Ejaculation

Paick JS, Jeong H, Park MS.
Int J Imp Res. 1998;10:247-250.

PE is the most common sexual dysfunction in men, affecting approximately 30% of men regardless of age.[1] One of the initial theories concerning the cause of this disorder was that the patient's penis was "very sensitive," triggering the ejaculatory response before the patient or his partner wished. Even though topical creams to "desensitize" the penis may be successful in improving the time to ejaculation,[2] Paick and colleagues recently demonstrated that penile sensitivity is probably not a contributing factor for PE. These authors used a vibrator in patients with PE and in controls without PE and showed that there was no difference between the groups in sensitivity of the glans, the shaft, or frenular area of the penis.

References

1. Laumann EO, Oaik A, Rosen RC. Sexual dysfunction in the US: prevalence and predictors. *JAMA.* 1999;281:537-544.
2. Choi HK, Xin ZC, Choi YD, et al. Safety and efficacy study with various doses of SS-cream in patients with premature ejaculation in a double-blind, randomized, placebo controlled clinical study. *Int J Imp Res.* 1999;11:261-264.

Cortical Evoked Responses From the Perineal Nerve

Uchio EM, Yang CC, Kromm BG, Bradley WE.
J Urol. 1999;162:1983-1986.

The major recent scientific finding involving PE is gleaned from the psychiatric literature: selective serotonin reuptake inhibitors (SSRIs) have a high incidence of anejaculation as one of their side effects. The exact mechanism of action of these drugs on the ejaculatory response is not known as yet, but recent electrophysiologic studies in men suggest that the pudendal nerve is probably involved. This is not surprising, since the musculature of the perineum and pelvis that is involved in the orgasmic phase of the ejaculatory response is known to be innervated by the pudendal nerve. For example, at the time of ejaculation, it is the contraction of the ischiocavernous muscles that surround the base of each corporal body that causes elevation of the intracorporeal pressure into the suprasystolic range (time of maximal rigidity of the penis during sexual activity); these